EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

PLANNED PARENTHOOD OF TENNESSEE AND NORTH MISSISSIPPI; *et al*., Plaintiffs, v. HERBERT H. SLATERY III, Attorney General of Tennessee; *et al.*, Defendants.	CIVIL ACTION CASE NO. 3:20-cv-00740 JUDGE CAMPBELL MAGISTRATE JUDGE NEWBERN

REBUTTAL DECLARATION OF COURTNEY A. SCHREIBER, M.D., M.P.H. IN SUPPORT OF PLAINTIFFS' MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

Courtney A. Schreiber, M.D., M.P.H., declares and states as follows:

1. I am over 18 years of age and competent to make this declaration.

2. I submit this declaration in response and rebuttal to the declarations of Drs. Donna Harrison, George Delgado, Brent Boles, Michael Podraza, and Martha Shuping, submitted by Defendants in support of their opposition to Plaintiffs' Motion for a Temporary Restraining Order and/or Preliminary Injunction of H.B. 2263/S.B. 2196 (the "Act").[1]

3. Nothing in Defendants' supporting declarations alters the fact that there is *no* reliable scientific evidence that progesterone increases the chances of continuing a pregnancy after

[1] I have not addressed every assertion and opinion contained in the declarations and other materials submitted by Defendants. The fact that I have not addressed a particular statement or assertion does not mean that I agree with the statement or assertion.

taking mifepristone. To force providers in Tennessee to steer patients toward a treatment that fundamentally lacks a basis in evidence is harmful to patients and the integrity of the medical profession.

Unproven Theories Are Insufficient to Justify Changes in Practice

4. In her declaration, Dr. Harrison repeatedly acknowledges that mifepristone reversal is not medically or scientifically proven, but instead merely "scientifically feasible." Resp. Opp'n Pls.' Mot. TRO/Prelim. Inj. ("Defs.' Br.") Ex. B, Decl. of Dr. Donna Harrison ("Harrison Decl.") ¶ 20, ECF No. 16-2. It is my opinion that this very uncertainty makes forcing physicians to inform their patients that medication abortion reversal "may be possible" a clear deviation from the standard of care and from beneficent medical care.

5. Dr. Harrison opines that medication abortion reversal makes biological sense, as it is "patterned after a known biological phenomenon which is a basic principle in biochemistry." *Id.* ¶ 13. Even if that were true (as I explain below, it is not), "reversal" would still be just a theory without medical evidence to support it. There are many medical and scientific theories that, even if they make some logical sense in theory, do not pan out in practice or in clinical studies. It is for this reason that methodical, scientific study of theories, including through clinical trials, is paramount to the safe practice of medicine. In this case, Dr. Harrison acknowledges that the scientific points she makes do not "prove" that reversibility is effective, *Id.* ¶ 20, but nevertheless opines that it is necessary to inform patients about the "possibility of reversal" in order for them to make an informed choice, *Id.* ¶ 48. To force providers to inform patients of a theoretical possibility when their well-being is at stake is inconsistent with the standard of care and potentially harmful.

6. Ensuring that a patient is informed before consenting to a medical procedure does not include informing that patient about every single fringe medical theory that has yet to be proven by sound medical evidence. For example, some people believe, despite a lack of evidence, that hypnotherapy can cure cancer, but this does not mean that oncologists should be forced to inform all their cancer patients that it may be possible to cure cancer with hypnotherapy. In fact, doing so given the current state of the evidence would be misleading. Legislating to force physicians to inform patients about unproven theories, especially when the proposed treatment may actually be harmful and costly to the patient, disrupts and impedes the patient-provider relationship and contravenes the true purpose of the informed consent process. Providing information on unproven or fringe theories during the informed consent process is not only unhelpful, but can also be harmful—it may result in patient confusion at the exact moment when clear thinking is required in order to make a decision.

7. Moreover, as noted in my initial declaration, Plaintiffs follow an evidence-based protocol for administering mifepristone, which involves the administration of mifepristone *in combination with* misoprostol. Mem. Law Supp. Mot. TRO/Prelim. Inj. ("Pls.' Br."). Ex. 1, Decl. of Courtney A. Schreiber M.D., M.P.H. ("Schreiber Decl.") ¶¶ 19, ECF No. 6-1. A physician providing medication abortion must provide the patient with the information she needs to give informed consent to undergo *that procedure*. The experimental administration of a high dosage of progesterone to "reverse" the effects of mifepristone would be a distinct medical procedure, involving a different combination of medications intended to achieve an entirely different result. It is simply inaccurate as a matter of medical practice or ethics to suggest that informing a patient about the latter procedure is necessary to obtain the patient's informed consent to the former.

8. Further, as I explained in my initial declaration (*id*. ¶¶ 76–78), medical providers in the United States currently cannot prescribe mifepristone (marketed under the name Mifeprex) from the manufacturer unless they agree to administer mifepristone as part of a medication regimen that also involves administration of the second medication in the medication abortion regimen, misoprostol. Mifepristone "reversal" treatment with progesterone is not an "alternative" to the FDA-approved protocol for administering mifepristone in combination with misoprostol. There is no evidence-based protocol for administering mifepristone without instructing patients to take the second drug, misoprostol. The medical alternatives to a medication abortion with mifepristone and misoprostol are a procedural abortion or continuing the pregnancy.

Progesterone Is Unlikely to "Reverse" the Effects of Mifepristone

9. As I explained in my initial declaration (*id*. ¶ 54), Drs. Harrison and Delgado's theory that exogenous progesterone can outcompete mifepristone is unlikely to be correct. Progesterone levels are already very high in pregnancy. Mifepristone already outcompetes these very high levels of the body's natural progesterone and binds tightly to progesterone receptors. Critically, mifepristone has a higher affinity for the receptors, meaning that mifepristone binds more tightly to the receptors than progesterone does—a fundamental point that Drs. Harrison and Delgado do not dispute or even attempt to address. Because of mifepristone's higher affinity for progesterone receptors, there is no reason to think that adding exogenous progesterone to the already very high levels of naturally-occurring progesterone would cause mifepristone to no longer bind to the receptors. Nor is there evidence to support such a theory.

10. In support of this theory, Dr. Harrison draws parallels to the use of other drugs in vastly different scenarios, arguing, for example, that the use of the drug leucovorin to "rescue" non-cancer cells from the effects of methotrexate (used to kill cancer cells) demonstrates the "basic medical principle" underlying medication abortion reversal. Harrison Decl. ¶ 15. However, Dr.

Harrison oversimplifies the science and draws inappropriate, misleading analogies. With regard to methotrexate specifically, Dr. Harrison fails to note that methotrexate is embryocidal, and commonly used to treat ectopic pregnancies. Leucovorin, often referred to as a "rescue" drug, is administered to help mitigate the side effects of methotrexate on other organ systems (such as repairing mouth sores). However, it does *not* "reverse" or counteract the embryocidal effect of the methotrexate on the ectopic pregnancy. Dr. Harrison's analogy to methotrexate and leucovorin thus completely undermines her hypothesis, as it shows that some effects of methotrexate can be counteracted, but its effects on a pregnancy are actually irreversible. Applying Dr. Harrison's analogy to the case of mifepristone reversal (using progesterone as the rescue medication) demonstrates that the effect of mifepristone on the pregnancy may *not* be reversed: despite the theoretical efficacy, leucovorin does not reverse methotrexate's effects on a pregnancy, and this may be the same for the mifepristone-progesterone combination. The bottom line is that we don't know, and we won't know unless appropriately-designed studies are conducted.

11. Drs. Harrison and Delgado also rely on a study of rats conducted in 1989 as evidence to support the use of progesterone to reverse the effects of mifepristone. Harrison Decl. ¶ 17; Defs.' Br. Ex. D, Decl. of Dr. George Delgado ("Delgado Decl.") ¶ 18, ECF No. 16-4. Their use of this study to support their reversal theory is so misleading that it undermines their credibility and calls into question their fidelity to basic scientific principles.

12. It is well known and understood that a study on rats (or animals generally[2]) is not sufficient to support a change in practice on humans. Researchers perform studies on rats to

[2] Another source Dr. Harrison cites examines the transformation of the rabbit uterine progesterone receptor following binding to several synthetic steroids. Harrison Decl. ¶ 11 (citing Charles H. Spilman et al., *Progestin and Antiprogestin Effects on Progesterone Receptor Transformation*, 24 J. Steroid Biochem. 383, 385–89 (Jan. 1986)).

generate hypotheses and candidates for study in humans. But many studies on rats have generated promising theories that later turn out not to be successful—or worse, turn out to be harmful—when studied in humans. This is precisely why human clinical trials are performed; we need evidence showing that a particular treatment is safe and effective *for humans* before clinicians begin providing their patients the treatment. This is a very basic principle. In addition, progesterone receptors vary widely between species in their affinities for different molecules,[3] making it even less appropriate to draw conclusions about the safety of a treatment for humans from a study of rats.

13. In addition, the rat study on which Drs. Harrison and Delgado rely does not show that the effects of mifepristone can be reversed in rats. The researchers were not investigating whether the effects of mifepristone can be reversed; instead, they were looking into the role of progesterone in maintenance of the pregnancy. Delgado Decl. Attach. 2 ("Yamabe Paper") at 1. The researchers injected one group of rats with mifepristone alone, a second group with mifepristone and progesterone, and a third group with ethanol (as a control). *Id*. at 3. The rats that were administered both mifepristone and progesterone appear to have received both substances at the same time. *Id.* The study therefore does not tell us anything about the rate of continued pregnancy in rats injected with progesterone *after* mifepristone has already taken effect. That is, it does not in any way address whether the effects of mifepristone can be "reversed" in rats—much less in humans.

[3] Etienne-Emile Baulieu, RU 486: *An Antiprogestin Steroid with Contragestive Activity in Women*, in THE ANTIPROGESTIN STEROID RU 486 AND HUMAN FERTILITY CONTROL 1, 5 (Etienne-Emile Baulieu and Sheldon J. Segal eds., 1985).

The "Case Studies" Cited by the State's Declarants Do Not Support a Change in Practice

14. Several of the State's Declarants rely heavily on, among other things, a 2018 paper to support their opinions regarding medication abortion reversal. I discussed that paper and a 2012 paper relied upon by some of the Declarants—both published by Drs. George Delgado and Mary Davenport—at length in my initial report. *See* Schreiber Decl. ¶¶ 29–49. Though I will not repeat those papers' extensive flaws here, I do note that several of the State's Declarants leave out key facts in their characterizations of the 2018 paper's findings.

15. For example, Dr. Brent Boles, in his testimony before the Tennessee General Assembly on the Act (attached to his declaration), stated that the 2018 paper "included 754 patients in whom the current recommended regimen had a 68 percent success rate at reversing the abortion process with no increased outcomes that were unfavorable for the mother or the baby. There were no birth defects. There were no other issues reported in that study." Defs.' Br. Ex. A, Decl. of Dr. Brent Boles ("Boles Decl.") Attach. 2 ("H. Comm. Hr'g") at 7:14–19, ECF No. 16-1. This statement misrepresents the Delgado paper and contains so many inaccuracies that it is worth addressing each in turn.

16. First, a number of patients were excluded from the paper for various reasons, leaving 547 patients, not 754, "with analyzable outcomes who underwent progesterone therapy." Schreiber Decl. Ex. C ("Delgado 2018 Paper") at 26. Thus, the suggestion that the Delgado paper reflected data from 754 patients is simply inaccurate.

17. Next, the paper did not find that 68% of patients remained pregnant after treatment. Rather, it found that, of the patients whose outcomes were analyzed, only 48% remained pregnant at twenty weeks. The 68% number is based on a substantially smaller subset of patients—only thirty-one—who received high-dose oral progesterone. *Id.* at 27. Notably, although the paper notes that "the gestational age at the time of ingestion was directly related to reversal success," it

provides no information about the gestational age of the pregnancies of the patients in this specific group. *Id.* at 26. The exclusion of this basic data from the paper makes it impossible to determine the relative likelihood that these patients would have continuing pregnancies after mifepristone anyway, in the absence of progesterone. This is significant because, as everyone appears to agree, mifepristone alone (without misoprostol) is less effective at ending pregnancies in later stages of gestation (although it is still highly effective when used in the mifepristone-misoprostol regimen). Thus, for example, if patients at later gestational ages were part of the high-dose oral progesterone group, the gestational age alone could account for the rate of continuing pregnancy.

18. Thirdly, the paper does not report that there were "no birth defects," as Dr. Boles testified, but rather reports seven, noting that this rate was equal to the birth defect rate in the general population. *Id*. at 28. Further, the paper did *not* show that there were no unfavorable outcomes for patients who received progesterone. To the contrary, the paper contains *no information* about any of the patients for whom "reversal" was not successful, meaning it is entirely unknown whether they suffered adverse events or not. For example, there is no discussion of whether any of these patients experienced a hemorrhage, which the prospective, controlled study conducted by Dr. Mitchell Creinin (discussed in my initial declaration, Schreiber Decl. ¶¶ 63–67) indicates may be a potential risk of taking mifepristone and not subsequently taking misoprostol. The paper's complete failure to follow up with or report any outcomes on patients for whom "reversal" was not successful wholly undermines any claim that the paper demonstrates that there were "no increased outcomes that were unfavorable" for the participants, H. Comm. Hr'g at 7:13–19, or even that the paper properly "analyzed safety," Harrison Decl. ¶ 28.

19. As I explained in my initial declaration, the 2018 paper likely overestimates the rate of success of the "reversal" treatment. Schreiber Decl. ¶ 43. In sum, patients in the paper were

administered progesterone only after an ultrasound was used to confirm ongoing fetal cardiac activity after taking mifepristone (except in an unknown number of instances in which pre-administration ultrasound was not readily available). This means that these pregnancies had already withstood the effects of the mifepristone for some period of time prior to the administration of progesterone. Thus, the paper did not analyze a representative sample of the population, but rather preemptively excluded patients whose pregnancies had already been terminated by mifepristone. Without a control group, there is no way to know whether these pregnancies simply did not abort from mifepristone alone (which we would expect since the regimen is a two drug regimen and only one was used) or the progesterone affected the lack of abortion efficacy.

20. Dr. Harrison claims that this criticism is "ludicrous" because the "whole point of the 2018 Delgado case series was to determine whether progesterone could keep a human embryo alive after exposure to mifepristone." Harrison Decl. ¶ 40 (emphasis omitted). This response misses the point. No one disputes that the intent of the providers administering progesterone was to facilitate an ongoing pregnancy. But that does not undermine the fact that the paper's population oversamples pregnancies that withstood the initial effects of mifepristone exposure—thus overstating the effects of the treatment. A biased sample population undermines the results of a study.

21. Moreover, Dr. Harrison fails to recognize that in order to actually examine the effectiveness of this treatment, a valid control group is necessary, which, as I discussed in my initial declaration, *see* Schreiber Decl. ¶¶ 41–42, 46–49, the 2018 Delgado paper lacks. In other words, if researchers are including only those pregnancies that have already survived the effects of mifepristone, there is no way to determine, without a valid control group, whether those pregnancies were predisposed to withstanding the effects of mifepristone. By not using a control

group, and confirming fetal cardiac activity prior to administration of progesterone, the authors have biased their study design to favor their hypothesis. This is not a reliable scientific methodology, and certainly not a basis to support a change in medical practice. Indeed, the authors of the paper recognize that this is a "confounding variable," but do not adequately account for its significance or attempt to statistically control for this as a confounding variable, as any valid scientific research study would do. Delgado 2018 Paper at 29.

22. I also disagree with Dr. Harrison's opinion that Dr. Delgado's 2018 paper has merit because he used a "historical control" group derived from a 2017 literature review. Harrison Decl. ¶¶ 24–25, 35. As I explained in my initial declaration, Dr. Delgado referred to his 2018 paper as a "case series."[4] Case series, by definition, do not include control groups.[5] They are used to identify new possible adverse effects of a drug or to identify a potential novel finding that the author is proposing for future study. However, they are not considered sufficient evidence to support the safety, efficacy, or utility of a new treatment, nor are they considered an appropriate basis for providing or recommending a new course of treatment.

23. Despite calling the 2018 paper a "case series," the authors nevertheless inappropriately attempt to draw causal conclusions from it, specifically by purportedly relying upon a historical control group. However, as I discussed extensively in my initial declaration, Schreiber Decl. ¶¶ 41–42, 46–49, neither of Dr. Delgado's medication abortion reversal papers had a scientifically valid control group, concurrent or historical. In my initial declaration, I described an appropriate historical control group for the case studies Dr. Delgado conducted, and

[4] As I explained in my initial declaration, Dr. Delgado's 2018 paper did not use an accepted or valid study design and cannot even fairly be categorized as a scientifically valid "case series." *See* Schreiber Decl. ¶ 41.

[5] Bauke Kooistra et al., *How to Design a Good Case Series*, 91 J. Bone & Joint Surgery 21, 21 (May 2009).

I explained the multiple flaws in Dr. Delgado's study design and the reasons the Davenport literature review is not an appropriate historical control. The assertion that using a concurrent control group is impossible is false, as I explain below.

24. In attempting to justify why no randomized controlled trials are necessary to support the adoption of a new treatment, the State's Declarants point to a study that actually demonstrates how a historical control group can be used in a reliable, scientific way—precisely the opposite of what Drs. Delgado and Davenport did in their 2018 paper. Harrison Decl. ¶¶ 36-37; Defs.' Br. Ex. J, Decl. of Dr. Martha Shuping ("Shuping Decl.") ¶¶ 136–141, 153, ECF No. 16-10. The Spitz et al. study, completed in 1988, involved the administration of 600 mg of mifepristone and 400 mcg of misoprostol two days later to 2121 patients seeking termination of their pregnancies of up to sixty-three days from their last menstrual period ("LMP").[6] The study found that the medication abortion regimen successfully terminated 92% of the pregnancies in patients at or under forty-nine days LMP, and concluded that the use of the regimen was safe and effective in that gestational age group.[7] Drs. Harrison and Shuping claim that this study, because it did not use a concurrent placebo control group, demonstrates that such a control group is not necessary to draw valid scientific conclusions and support changes in practice. Harrison Decl. ¶¶ 36-37; Shuping Decl. ¶¶ 136–141, 153. But in the case of the Spitz study, there is a substantial historical control group—an enormous number of women over a substantial period of time who have been pregnant up through forty-nine days LMP and who do not take mifepristone and/or misoprostol. The rate of spontaneous abortion for patients in this group over a limited time period (study participants were followed for fifteen days) is nowhere near 92%. Thus, compared to this

[6] Irving M. Spitz et al., *Early Pregnancy Termination with Mifepristone and Misoprostol in the United States*, 338 N. Eng. J. Med. 1241, 1241 (Apr. 1998).
[7] *Id.*

historical control group, an intervention that terminates a pregnancy 92% of the time has clearly demonstrated its efficacy. As I noted in my initial declaration, a historical control group can be used to draw potential conclusions about the efficacy of a proposed treatment only where, as in the Spitz et al. study, the researchers find a vastly larger difference in outcome between the historical control group and the treatment group than they would look for in a study using a concurrent control group. An abortion rate of 92% after taking mifepristone and misoprostol would certainly qualify, allowing the researchers to conclude that the medication abortion regimen was safe and effective in patients who were up to forty-nine days LMP.

25. In the 2018 Delgado paper, by contrast, there is no such large historical population of pregnant patients who have taken mifepristone but not misoprostol to whom the "reversal" treatment (administering progesterone) can be compared. In fact, even the data relied upon by the State's Declarants, such as the Delgado and Davenport papers, varies widely. It is not scientifically feasible, or responsible, to draw conclusions about medication abortion "reversal" based on the purported use of a historical control group when there is no reliable one to use. The Spitz et al. study, rather than strengthening the Declarants' arguments, illustrates the proper use of a historical control group, in stark contrast to the Delgado papers that use said type of group improperly, for the reasons I discussed in my initial declaration. Schreiber Decl. ¶¶ 47–49.

26. At any rate, none of the Defendants' Declarants undermine my criticism of the Delgado papers. They do not provide any basis for physicians to change their practice and begin recommending or endorsing the administration of progesterone after mifepristone to "reverse" the abortion process.

27. Drs. Harrison and Delgado also take issue with a systematic review of the research on mifepristone "reversal," published in 2015 by Dr. Daniel Grossman and several other

researchers, which demonstrated that the evidence is insufficient to determine whether treatment with progesterone after mifepristone results in a higher proportion of continuing pregnancies compared to expectant management. *See* Schreiber Decl. Ex. F ("Grossman 2015"). Specifically, they criticize the review for (1) failing to include five "critical" studies that documented embryo survival after taking mifepristone, and (2) including four studies that did not assess abortion failure using ultrasound. Delgado Decl. ¶¶ 35–36; *see also* Harrison Decl. ¶ 38. They rely instead on a "systematic review" published in 2017 by Drs. Delgado and Davenport. I have already explained why this paper is flawed in a number of key ways, including the exclusion of certain studies with no explanation and the use of selective reporting. *See* Schreiber Decl. ¶ 51.

28. With regard to the studies that Drs. Harrison and Delgado criticize Dr. Grossman for excluding, an examination of the Davenport and Delgado 2017 review makes clear that those studies involved the administration of high doses of mifepristone, generally 800 to 1000 mgs, which is four to five times higher than the 200 mg of mifepristone administered as part of the standard medication abortion regimen. Rather than being "critical," as Dr. Delgado claims (Delgado Decl. ¶ 35), these studies in fact are the *least* relevant to the provision of medication abortion in a clinic setting today.

29. Dr. Harrison criticizes Dr. Grossman for including in his analysis four studies that supposedly "did not assess embryo survival at all." Harrison Decl. ¶ 38. That is incorrect. Dr. Grossman specifically "excluded studies that only reported medical abortion failure after mifepristone alone and did not specify the number of continuing pregnancies." Grossman 2015 at 207.

30. Dr. Delgado similarly criticizes Dr. Grossman for including "four studies that did not assess abortion failure using ultrasound." Delgado Decl. ¶ 35. One of those studies is the Zheng

study, which contains the largest population dataset among the studies of patients who took only mifepristone, and which reports a 46% rate of continuing pregnancy after patients took mifepristone alone.[8] Grossman 2015 at 208. The author of this study classified pregnancies as ongoing based on hCG serum levels, absence of expelled uterine contents, and uterine size.[9] But studies that Dr. Delgado chose to include in his analysis employ *identical* criteria.[10] By applying exclusion criteria in an uneven manner to pick and choose among studies, Dr. Delgado highlights the inconsistencies in the data, further demonstrating the conclusion that the available information is insufficient to alter the current practice.

31. Dr. Harrison likewise cites a **three-person** case series from Australia to support her theory about medication abortion "reversal." Harrison Decl. ¶ 18. But this paper is just as flawed as the others. As Dr. Harrison admits, that paper has a sample size of only three patients. A paper with such a tiny sample size does not provide a basis to draw any conclusions about the safety or efficacy of medication abortion "reversal."

Ethical Study of Medication Abortion Reversal Is Both Possible and Necessary to Justify Any Change in Practice

32. I further disagree with Drs. Harrison, Delgado, and Shuping's opinions on the feasibility of ethically studying medication abortion "reversal." For example, while Dr. Shuping acknowledges that the "gold standard" for assessing safety and efficacy of medications is the placebo-controlled, randomized clinical trial, she opines that ethical research on the use of

[8] Zheng Shu-Rong, *RU 486 (Mifepristone): Clinical Trials in China*, 149 Act Obstetricia Gynecologica Scan. Suppl. 19, 21 (1989).
[9] *Id.*, at 20.
[10] *See, e.g.*, Laszlo Kovacs, et al., *Termination of Very Early Pregnancy by RU 486 – An Antiprogestational Compound*, 29 Contraception 399, 401 (1984) ("If at the 14-day visit, the plasma B-hCG exceeded 2000 IU/l, it was assumed that the pregnancy was continuing. . . ."). This study is cited in Mary L. Davenport et al., *Embryo Survival After Mifepristone: Review of the Literature*, 32 Issues in Law & Med. 3, 14 (Nov. 2017).

progesterone to "reverse" mifepristone is impossible. *See* Shuping Decl. ¶¶ 129, 142–160; *see also* Harrison Decl. ¶ 37; Delgado Decl. ¶ 42.

33. It is certainly possible to conduct an ethical placebo-controlled, randomized clinical trial of the use of progesterone to "reverse" the effects of mifepristone: researchers could design studies where the participants properly consented to experimental treatment according to a standard progesterone protocol. And not only is it possible, but it also has already been done. As I explained in my initial declaration (Schreiber Decl. ¶¶ 63–67), the study conducted by Dr. Creinin was a randomized, double-blind, placebo-controlled trial designed to evaluate continuing pregnancy rates, safety, and side effects of high-dose oral progesterone in patients who used mifepristone alone without misoprostol. Critically, this study had Institutional Review Board ("IRB") approval, meaning it was approved by a committee that performs ethical reviews of proposed research on human subjects to protect the participants.

34. The State's Declarants' positions regarding how to conduct ethical studies are even more unreasonable in light of the fact that Dr. Delgado's 2018 paper, upon which Drs. Harrison, Delgado, and Shuping rely heavily as evidence that medication abortion reversal works, was temporarily removed at the request of the University of San Diego's IRB because it contained misleading information regarding the paper's IRB approval. Schreiber Decl. ¶¶ 40–41. All human subject research, including case studies, should be approved by an IRB before the research is conducted to ensure that such research is ethical. The professional norm and expectation is that research on human subjects undergoes IRB review in order to protect the participants and serve as an important quality control mechanism. Offering experimental care without proper institutional oversight, as Dr. Delgado appears to have done, is not only unethical research on human subjects, but also undermines researchers' ability to perform ethical research, as patients will be less inclined

to enroll in research-generating studies if they can obtain the same experimental treatment outside the research setting.

Dr. Delgado Misrepresents the Results and Conclusions from the Only Prospective, Controlled Study of the "Reversal" Theory

35. As I discussed in my initial declaration, Schreiber Decl. ¶¶ 63–67, the researchers led by Dr. Creinin halted their prospective, controlled study after enrolling only twelve participants, due to serious safety concerns with continuing the study, because three of the twelve participants had severe, brisk hemorrhaging and had to be taken by ambulance to an emergency room. One of the three patients came from the progesterone population, and two came from the placebo population. The fact that the patients with hemorrhaging came from both populations suggests that the hemorrhaging resulted from not following the medication abortion two-drug regimen—which is exactly what Tennessee would require that physicians tell patients is an option to consider. The study thus raises the possibility of serious safety concerns about not completing the medication abortion two-drug combination regimen.[11]

36. Dr. Delgado misrepresents important aspects of this study. He states that the study showed that "mifepristone alone for abortion was unsafe" but "attempting reversal was not proven to be unsafe." Delgado ¶ 32. However, the "reversal" hypothesis involves patients taking mifepristone and not misoprostol. Therefore, the experiences of the patients who took mifepristone and not misoprostol are all relevant to the safety of medication abortion "reversal." Three of the twelve patients who took mifepristone and not misoprostol had such severe bleeding that they were transported by ambulance to the emergency room, and one had to have a blood transfusion. The sample size is too small to quantify the extent of the risk of hemorrhaging. But the study does show

[11] Mitchell D. Creinin, et al., *Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial*, 135 Obstetrics & Gynecology 158 (Jan. 2020).

that there are "potential dangers for patients who opt not to use misoprostol after mifepristone ingestion."[12]

37. Further, Dr. Delgado's assertion that the study showed that "attempting reversal was not proven to be unsafe" is not a reliable scientific approach, or a sufficient basis to justify a change in practice. The study did not demonstrate the efficacy of "reversal" treatment with progesterone. Physicians do not provide treatments to patients based on a demonstration that they are not "unsafe"; rather, a novel or experimental treatment must be proven safe and effective, generally using larger data sets with more rigorous study methodologies that include a sample size calculation and a control group, in order to justify a recommended practice change.

Safety of Progesterone

38. Dr. Harrison incorrectly claims that based on animal studies, anecdotal and/or scientifically invalid evidence of mifepristone "reversal" with progesterone, and the fact that progesterone is commonly prescribed to people early in pregnancy (specifically for patients who become pregnant by in-vitro fertilization or have progesterone deficiencies), it is "scientifically proper" to administer high doses of exogenous progesterone to patients. Harrison Decl. ¶¶ 29–31. However, it is common knowledge within the medical profession that excessively large exogenous doses of any naturally occurring chemical, including water and Vitamin C, can be risky or even dangerous.

39. Further, virtually any drug can cause an adverse reaction, so any time an intervention is suggested by a health care provider, the expectation on the part of the patient is that there is a reason for this recommendation: i.e., some clear evidence of efficacy. Because the use of progesterone to "reverse" abortion has not been proven safe, and because there is an absence of

[12] *Id.,* at 162.

data on its efficacy for this purpose, it is my opinion that exposing patients to this treatment as a matter of course is unethical.

40. Dr. Harrison also mischaracterizes the discussion in my initial declaration, *see* Schreiber Decl. ¶ 59, about studies that raised concerns regarding certain exogenous progesterone preparations. Harrison Decl. ¶ 30; *see also* Delgado Decl. ¶ 9. It is my understanding that the Act requires physicians to direct patients to the Tennessee Department of Health website, which must post information on and assistance with the resources that may be available to help reverse the effects of a chemical abortion. Other than the two published Delgado papers, the only other source for information supporting medication abortion "reversal" about which I am aware is the "Abortion Pill Rescue" ("APR") hotline and website that I discussed in my initial declaration. *See* Schreiber Decl. ¶¶ 56–58. To my knowledge, the APR hotline and website has never publicized the delivery system or name of the compound they recommend for "reversal" treatment with progesterone. There is an extensive range of natural and synthetic progesterone compounds available on the market; because, to my knowledge, no evidence-based protocol currently exists, there is no way to know what drug treatments providers are using for "reversal." Given the ready availability of both natural and synthetic progesterone, and the lack of information about the manner in which APR-affiliated individuals are providing "reversal" treatment, I believe there is a potential for harm and that studies on the potential risks of both natural and synthetic progesterone are relevant at this time.

The Act's Mandatory Disclosures are Inconsistent with Professional and Medical Ethics and Damage the Provider-Patient Relationship

41. I agree with Dr. Delgado that providers have an ethical responsibility to provide important information to patients seeking medication abortion. Delgado Decl. ¶ 43. As I explained in my initial declaration, the true purpose of the informed consent process is to give each patient

medical information relevant to their healthcare decision-making in a way that is easy to absorb and understand—i.e., that is clear, concise, and applicable to her circumstances and individual concerns. However, information about medication abortion reversal, an unproven, experimental treatment, not only does not qualify as relevant, important information for patients seeking medication abortion, but also actively undermines the informed consent process. The state-mandated messages around medication abortion reversal create a real risk that a patient might begin the medication abortion process before she was ready to do so, under the mistaken impression that she could always change her mind after taking mifepristone. In this way, the state-mandated messages hinder the physician's efforts to ensure that the patient does not begin pregnancy termination treatment unless they are certain about their decision to end the pregnancy. This is contrary to the most fundamental tenets of medicine.

42. As I explained in my initial declaration, I do not believe the problems created by forcing providers to repeatedly endorse experimental treatment can be solved by the providers' disavowal of the state-mandated messages. As an abortion provider, if I were forced to deliver a state-mandated message about experimental medical treatment and then tried to explain that what I just told the patient was untrue, misleading, and/or not relevant at all to the patient, that would increase patient confusion and make it harder for me to ensure that the patient understood all the relevant facts she needed to make an informed decision about whether or not to proceed with an abortion in the first place. This is similarly true with regard to any type of medical care I am providing for a patient. As I discussed in my initial declaration, *see* Schreiber Decl. ¶¶ 77–79, it would be particularly confusing for a patient obtaining a medication abortion in light of the fact that I am also required by the FDA to obtain the patient's signature on an agreement stating that

the patient will take both mifepristone and misoprostol. It could also lead a patient not to trust any of the information I gave her.

Dr. Shuping's Opinions

43. Given time constraints, I have not responded to each of the wide variety of opinions offered in Dr. Shuping's declaration, but it is important to address three points. First, I note that Dr. Shuping acknowledges that she is a psychiatrist and will therefore "assume that safety and efficacy [of medication abortion reversal] are adequate, with the expectation that questions regarding safety and efficacy must be resolved by OB/GYN experts or experts who provide this treatment." Shuping Decl. ¶ 102. Nevertheless, this does not prevent her from subsequently opining at length about the reliability and validity of the 2018 Delgado paper, even going beyond the authors' and other declarants' conclusions to state that, when combining (without any explanation or analysis of why this combination is appropriate) the rates of survival among three distinct sub-groups totaling 38 women who received at least 6 or more progesterone injections, "92% of these children survived." *Id.* ¶ 133. Beyond all the flaws in the paper that I outlined above, *see supra* ¶¶ 21–27, I note that the table upon which Dr. Shuping appears to rely in drawing this conclusion contains no information about the amount of progesterone administered, the time period over which it was administered, and the gestational age of the patients in each group.

44. Dr. Shuping also misrepresents the requirements of the Act, stating that it involves "two essential pieces of information": (1) a statement that "mifepristone alone is not always effective in ending a pregnancy," and (2) a statement that "[i]t may be possible to avoid, cease, or even reverse the intended effects of a chemical abortion utilizing mifepristone if the second pill has not been taken. Please consult with a healthcare professional immediately." *Id.* ¶¶ 109, 113. Her analysis of the "essential" parts of the Act appears to cover only the signage and written

discharge instruction requirements, and she ignores the mandatory disclosures that providers must give 48 hours prior to administering mifepristone to any medication abortion patient. *See* Tenn. Code Ann. § 39-15-218. She also fails to accurately describe the signage and written discharge instruction requirements; the first required statement, in its entirety, reads: "Recent developing research has indicated that mifepristone alone is not always effective in ending a pregnancy." Tenn. Code Ann. §§ 39-15-218(b),(f). Dr. Shuping has omitted the first part of the sentence, which, as I explained in my initial declaration, makes the statement inaccurate and misleading by implying that researchers have recently discovered that mifepristone is not as effective as previously believed, which is wholly untrue. Schreiber Decl. ¶ 74.

45. Further, I understand that Dr. Shuping makes a series of claims concerning the effects of abortion on mental health. The National Academies of Sciences, Engineering, and Medicine, a respected private nonprofit institution established by Congress to provide independent, objective analysis and advice to the public on scientific and medical issues, has engaged in a comprehensive review of the literature on this topic and has roundly rejected any association between negative mental health outcomes and abortion, noting that "having an abortion does not increase a woman's risk of . . . mental health disorders," including depression, anxiety, or post-traumatic stress disorder.[13] The American Psychological Association has also conducted an extensive review of the scientific literature on abortion and mental health and found that, "among women who have a single, legal, first-trimester abortion of an unplanned pregnancy. . . the relative

[13] Nat'l Acads. Sci., Eng'g, & Med., *The Safety and Quality of Abortion Care in the United States*, 10 (2018).

risks of mental health problems are no greater than the risks among women who deliver an unplanned pregnancy."[14]

I declare under penalty of perjury that the foregoing is true and correct.

Dated this 23rd day of September, 2020.

Courtney A. Schreiber, M.D., M.P.H.

[14] Am. Psych. Assoc. Task Force on Mental Health & Abortion, *Report of the APA Task Force on Mental Health and Abortion*, 92 (2008).